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(54) Title: PIPERIDINYL AND PIPERAZINYL SUBSTITUTED BENZOFUSED LACTAMS

(57) Abstract: Disclosed are piperidinyl and piperazinyl substituted benzofused lactam compounds which are useful for the treatment and/or prevention of neuropsychological disorders including, but not limited to, schizophrenia, mania, dementia, depression, anxiety, compulsive behavior, substance abuse, Parkinson-like motor disorders and motion disorders related to the use of neuroleptic agents. Pharmaceutical compositions, including packaged pharmaceutical compositions, are further provided. Compounds of the invention are also useful as probes for the localization of dopamine receptors in tissue samples.

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Piperidinyl and Piperazinyl Substituted Benzofused LactamsBACKGROUND OF THE INVENTION

This application claims priority to U.S. Provisional
5 Application no. 60/139,187 and U.S. Application Serial No.
09/333,368, both of which were filed on June 15, 1999, and each
of which is hereby incorporated by reference in its entirety.

Field of the Invention

10 This invention relates to piperidinyl and piperazinyl
substituted benzofused lactams, and to that that bind to
dopamine receptors. This invention also relates to
pharmaceutical compositions comprising such compounds and to
the treatment of central nervous system (CNS) diseases,
15 particularly the treatment or prevention of psychotic disorders
such as schizophrenia. Additionally this invention relates to
the use ligands for dopamine receptors as probes for the
localization of dopamine receptors in tissue sections.

20 Description of the Related Art

The therapeutic effect of conventional antipsychotics,
known as neuroleptics, is generally believed to be exerted
through blockade of dopamine receptors. However, neuroleptics
are frequently responsible for undesirable extrapyramidal side
25 effects (EPS) and tardive dyskinesias, which are attributed to
blockade of D₂ receptors in the striatal region of the brain.
The dopamine D₄ receptor subtype has been identified and
cloned. Its unique localization in limbic brain areas and its
differential recognition of various antipsychotics suggest that
30 the D₄ receptor may play a major role in the etiology of
schizophrenia. The dopamine D₄ receptor shares sequence
homology with dopamine D₂ and D₃ receptors, however the D₄
receptor possesses a unique pharmacological profile. Selective
D₄ antagonists, including the marketed antipsychotic

chlozapine, are considered effective antipsychotics free from the neurological side effects displayed by conventional neuroleptics. Compounds that possess a 10-fold or more higher affinity for dopamine D₄ receptors than D₂ receptors are considered particularly desirable as antipsychotics.

Since dopamine D₄ receptors are concentrated in the limbic system which controls cognition and emotion, compounds which interact with these receptors have utility in the treatment of cognitive disorders. Such disorders include the cognitive deficits which are a significant component of the negative symptoms (social withdrawal and unresponsiveness) of schizophrenia. Other disorders involving memory impairment or attention deficit disorder can also be treated with compound that interact specifically with the dopamine D₄ receptor subtype.

SUMMARY OF THE INVENTION

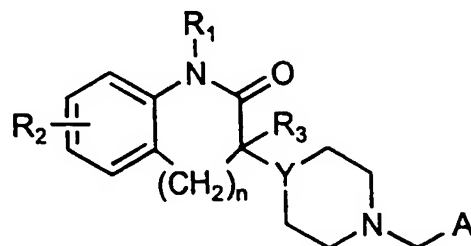
This invention provides piperidinyl and piperazinyl substituted benzofused lactam compounds that bind with high affinity and selectivity to binding to the D₄ receptor subtype, including human D₄ receptors. These compounds are therefore useful in treatment of a variety of neuropsychological disorders, such as, for example, schizophrenia, psychotic depression and mania. Other dopamine-mediated diseases such as Parkinsonism and tardive dyskinesias can also be treated directly or indirectly by modulation of D₄ receptors.

Thus, the invention provides compounds of Formula I (shown below), and pharmaceutical compositions comprising compounds of Formula I.

The invention further comprises methods of treating patients suffering from CNS disorders with a therapeutically effective amount of a compound of the invention. The patient may be a human or other mammal. Treatment of humans, domesticated companion animals (pets) or livestock animals suffering from CNS disorder with an effective amount of a compound of the invention is encompassed by the invention. Particularly methods for the treatment and/or prevention of neuropsychological or affective disorders, for example, schizophrenia, mania, dementia, depression, anxiety, compulsive behavior, substance abuse, memory impairment, cognitive deficits, Parkinson-like motor disorders, e.g., Parkinsonism and dystonia, and motion disorders related to the use of neuroleptic agents are included. In addition, the compounds of the invention are useful in treatment of depression, memory-impairment or Alzheimer's disease by modulation of D₄ receptors which selectively exist in limbic area known to control emotion and cognitive functions. Further, the compounds of the present invention are useful for the treatment of other disorders that respond to dopaminergic blockade, e.g., substance abuse and obsessive compulsive disorder. These compounds are also useful

in treating the extrapyramidal side effects associated with the use of conventional neuroleptic agents.

Accordingly, a broad aspect of the invention is directed to compounds of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

A represents phenyl, optionally substituted with up to four substituents selected from halogen, hydroxy, amino, mono- or di(C₁-C₆)hydrocarbylamino, aminosulfonyl, C₁-C₆ hydrocarbylaminosulfonyl, di(C₁-C₆)hydrocarbylaminosulfonyl, cyano, nitro, C₃-C₇ cyclohydrocarbyl(C₁-C₆)hydrocarbyl, trifluoromethyl, C₁-C₆ hydrocarbyl, trifluoromethoxy, C₃-C₇ cyclohydrocarbyl, and C₁-C₆ alkoxy;

R₁ is hydrogen, C₃-C₇ cyclohydrocarbyl(C₁-C₆)hydrocarbyl, C₁-C₆ hydrocarbyl, or C₂-C₆ alkanoyl;

R₃ is hydrogen, C₁-C₆ alkoxy carbonyl, aryloxy carbonyl, carboxyl, carboxamido, mono or di(C₁-C₆)hydrocarbylamino carbonyl, aryl(C₁-C₆)hydrocarbyl, or C₁-C₆ hydrocarbyl;

R₂ represents hydrogen, halogen, hydroxy, amino, mono- or di(C₁-C₆)hydrocarbylamino, aminosulfonyl, mono or di(C₁-C₆)hydrocarbylaminosulfonyl, cyano, nitro, C₃-C₇ cyclohydrocarbylhydrocarbyl, trifluoromethyl, C₁-C₆ hydrocarbyl, trifluoromethoxy, C₃-C₇ cyclohydrocarbyl, and C₁-C₆ alkoxy;

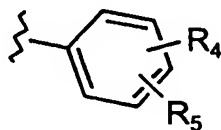
n is 0 or an integer chosen from 1 or 2;

Y is nitrogen or CH.

DETAILED DESCRIPTION OF THE INVENTION

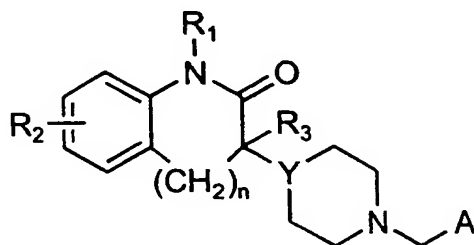
The invention encompasses the compounds of Formula I described above.

Preferred compounds of Formula I include those where A is
 5 a group of the formula:



wherein R_4 and R_5 independently represent hydrogen halogen, hydroxy, amino, mono- or di(C_1 - C_6)alkylamino, aminosulfonyl, C_1 - C_6 alkylaminosulfonyl, di(C_1 - C_6)alkylaminosulfonyl, cyano,
 10 nitro, cycloalkylalkyl, trifluoromethyl, C_1 - C_6 alkyl, trifluoromethoxy, C_3 - C_6 cycloalkyl, and C_1 - C_6 alkoxy.

Other preferred compounds of Formula I are those of formula II:



II

where

A represents phenyl, optionally substituted with up to four
 substituents selected from halogen, hydroxy, amino, mono-
 20 or di(C_1 - C_6)alkylamino, aminosulfonyl, C_1 - C_6 alkylaminosulfonyl, di(C_1 - C_6)alkylaminosulfonyl, cyano, nitro, cycloalkylalkyl, trifluoromethyl, C_1 - C_6 alkyl, trifluoromethoxy, C_3 - C_6 cycloalkyl, and C_1 - C_6 alkoxy;

R_1 is hydrogen, cycloalkylalkyl, C_1 - C_6 alkyl, or C_1 - C_6 alkanoyl;

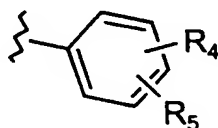
25 R_3 is hydrogen, alkoxycarbonyl, aryloxycarbonyl, carboxyl, carboxamido, mono or dialkylaminocarbonyl, arylalkyl, or C_1 - C_6 alkyl;

R₂ represents hydrogen, halogen, hydroxy, amino, mono- or di(C₁-C₆)alkylamino, aminosulfonyl, mono or di(C₁-C₆)alkylaminosulfonyl, cyano, nitro, cycloalkylalkyl, trifluoromethyl, C₁-C₆ alkyl, trifluoromethoxy, C₃-C₇ cycloalkyl, and C₁-C₆ alkoxy;

n is 0 or an integer chosen from 1 or 2;

Y is nitrogen or CH.

Preferred compounds of Formula II include those where A is a group of the formula:



wherein R₄ and R₅ independently represent hydrogen halogen, hydroxy, amino, mono- or di(C₁-C₆)alkylamino, aminosulfonyl, C₁-C₆ alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, cyano, nitro, cycloalkylalkyl, trifluoromethyl, C₁-C₆ alkyl, trifluoromethoxy, C₃-C₆ cycloalkyl, and C₁-C₆ alkoxy.

More preferred compounds of Formula II are those wherein n is 1;

R₁ is C₁-C₃ alkyl;

R₂ and R₃ are independently hydrogen or C₁-C₆ alkyl;

R₄ and R₅ are independently hydrogen, halogen, C₁-C₆ alkyl, or C₁-C₆ alkoxy, provided that not both R₄ and R₅ are hydrogen.

In these more preferred Formula II compounds, R₂ and R₃ are most preferably both hydrogen.

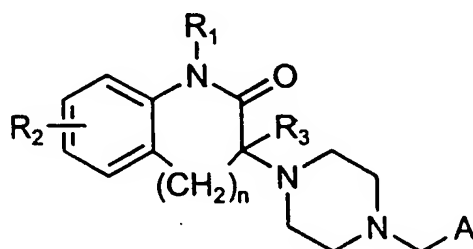
Other more preferred compounds of Formula II are those where R₁ is C₁-C₂ alkyl. A particularly preferred R₁ group is methyl. In the more preferred compounds of Formula II, R₄ and

R_5 are independently hydrogen, chloro, fluoro, bromo, C_1 - C_3 alkyl, or C_1 - C_3 alkoxy.

Particularly preferred compounds of II are those where both R_4 and R_5 are not hydrogen simultaneously.

5

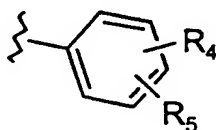
Other preferred compounds of Formula I are those of formula III:



III

10 where R_1 , R_2 , R_3 , A , and n are as defined above for Formula I.

Preferred compounds of Formula III include those where A is a group of the formula:



15 wherein R_4 and R_5 independently represent hydrogen halogen, hydroxy, amino, mono- or di(C_1 - C_6)alkylamino, aminosulfonyl, C_1 - C_6 alkylaminosulfonyl, di(C_1 - C_6)alkylaminosulfonyl, cyano, nitro, cycloalkylalkyl, trifluoromethyl, C_1 - C_6 alkyl, trifluoromethoxy, C_3 - C_6 cycloalkyl, and C_1 - C_6 alkoxy.

20

More preferred compounds of Formula III are those wherein n is 1;

R_1 is C_1 - C_3 alkyl;

R_2 and R_3 are independently hydrogen or C_1 - C_6 alkyl;

25 R_4 and R_5 are independently hydrogen, halogen, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy, provided that not both R_4 and R_5 are hydrogen.

In these more preferred Formula III compounds, R_2 and R_3 are most preferably both hydrogen.

5 Other more preferred compounds of Formula III are those where R_1 is C_1 - C_2 alkyl. A particularly preferred R_1 group is methyl. In the more preferred compounds of Formula III, R_4 and R_5 are independently hydrogen, chloro, fluoro, bromo, C_1 - C_3 alkyl, or C_1 - C_3 alkoxy.

10 Particularly preferred compounds of III are those where both R_4 and R_5 are not hydrogen simultaneously.

In other particularly preferred compounds of Formula III,
n is 1 or 2;
15 R_1 is C_1 - C_3 alkyl;
 R_2 and R_3 are hydrogen;
 R_4 and R_5 are independently hydrogen, halogen, C_1 - C_6 alkyl, or
 C_1 - C_6 alkoxy, provided that not both R_4 and R_5 are
hydrogen.

20

In these particularly preferred compounds of Formula III,
 R_1 is C_1 - C_2 alkyl. Still more preferably, R_1 in these compounds
is methyl.

25 Still other particularly preferred compounds of Formula III are those where R_4 and R_5 independently hydrogen, chloro, fluoro, bromo, C_1 - C_3 alkyl, or C_1 - C_3 alkoxy, R_1 is methyl, R_3 is hydrogen and n is 2. In these particularly preferred compounds of Formula III, R_4 and R_5 are not both hydrogen simultaneously.

30

More preferred compounds of Formula III are those wherein
n is 2;
 R_1 is C_1 - C_3 alkyl;
 R_2 and R_3 are independently hydrogen or C_1 - C_6 alkyl;

R_4 and R_5 are independently hydrogen, halogen, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy, provided that not both R_4 and R_5 are hydrogen.

- 5 In these more preferred Formula III compounds, R_2 and R_3 are most preferably both hydrogen.
- Other more preferred compounds of Formula III are those where R_1 is C_1 - C_2 alkyl. A particularly preferred R_1 group is methyl.
- 10 In the more preferred compounds of Formula III, R_4 and R_5 are independently hydrogen, chloro, fluoro, bromo, C_1 - C_3 alkyl, or C_1 - C_3 alkoxy.

Particularly preferred compounds of III are those where both R_4 and R_5 are not hydrogen simultaneously.

15

In other particularly preferred compounds of Formula III, n is 0;

R_1 is C_1 - C_3 alkyl;

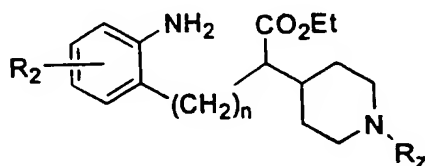
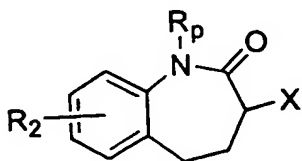
R_2 and R_3 are independently hydrogen or C_1 - C_2 alkyl;

- 20 R_4 and R_5 are independently hydrogen, halogen, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy, provided that not both R_4 and R_5 are hydrogen.

- In these particularly preferred compounds of Formula III, R_2 and R_3 are both hydrogen. Even more preferably, R_1 in these compounds is C_1 - C_2 alkyl. Still more preferably, R_1 in these compounds is methyl.

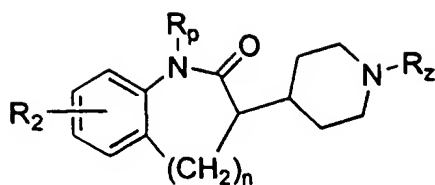
The invention also provides intermediates useful in preparing compounds of Formula I. These intermediates have

- 30 Formula IV, V, and VI.



IV

V



VI

5 In Formulas IV, V, and VI, R_2 , and n are as defined for Formula I. R_p is hydrogen, a nitrogen protecting group or R_1 . R_z is hydrogen, a nitrogen protecting group or $-CH_2-A$, wherein A is defined in Formula I. X is a leaving group, such as, for example, chloro, bromo, iodo.

10 The compounds of this invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, mixtures of diastereomers, or racemates or resolved enantiomers. Single enantiomers can be obtained as pure
15 compounds or in enantiomeric excess by asymmetric synthesis or by resolution of the racemate. Resolution of the racemate can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

20 Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table I and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base
25 can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance
30 with conventional procedures for preparing acid addition salts from base compounds.

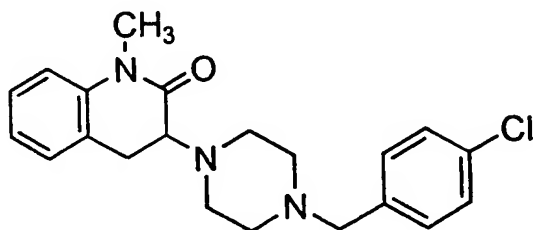
Non-toxic pharmaceutically acceptable salts include, but are not limited to salts with inorganic acids such as hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic, and nitric or salts with an organic acids such as formic, citric, malic, maleic, fumaric, tartaric, succinic, acetic, lactic, methanesulfonic, p-toluenesulfonic, 2-hydroxyethylsulfonic, salicylic and stearic. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses prodrugs of the compounds of Formula I, e.g., acylated compounds and esters of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and prodrugs of the compounds encompassed by Formula I.

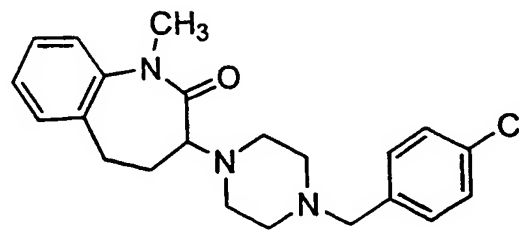
Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers. The invention includes all tautomeric forms of a compound.

Representative compounds of the invention are shown below in Table 1.

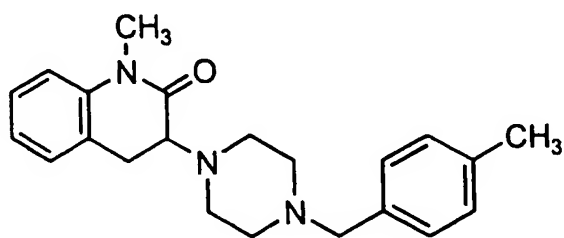
Table 1



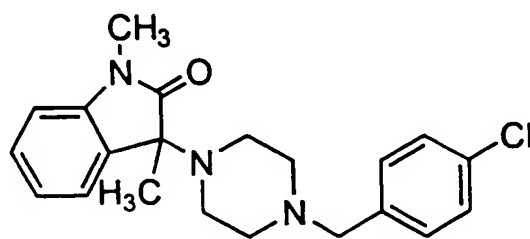
Compound 1a



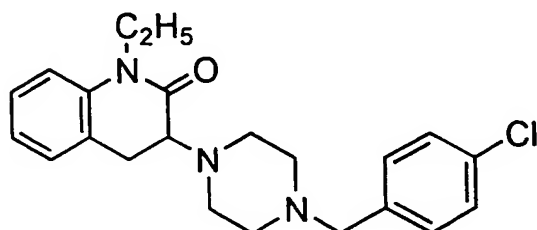
Compound 1e



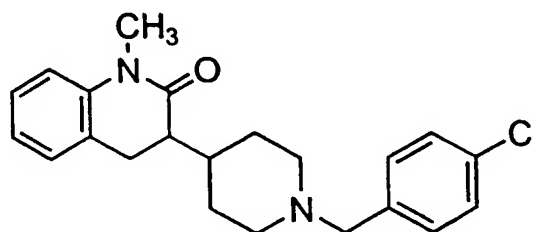
Compound 1b



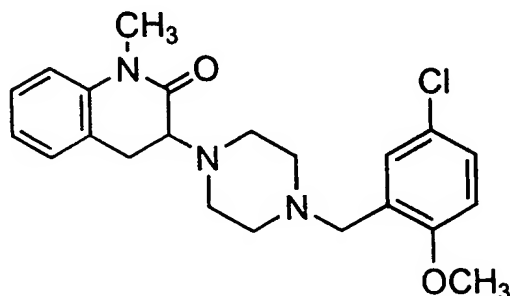
Compound 1f



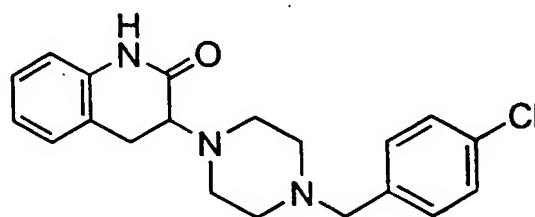
Compound 1c



Compound 1g



Compound 1d



Compound 1h

This invention relates to piperidinyl and piperazinyl substituted benzofused lactams that bind with high affinity to the dopamine receptors, particularly dopamine D₄ receptors, including human dopamine D₄ receptors. This invention also includes such compounds that bind with high selectivity to the dopamine receptors, particularly dopamine D₄ receptors, including human dopamine D₄ receptors. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula I with the dopamine D₄

receptor results in the pharmaceutical utility of these compounds.

The invention further comprises methods of treating patients suffering from CNS disorders with an amount of a
5 compound of the invention sufficient to alter the symptoms of the disorders.

The diseases, conditions or disorders that can also be treated using compounds and compositions according to the invention include, but are not limited to, schizophrenia,
10 psychotic depression, mania, and the extrapyramidal side effects associated with the use of a neuroleptic agent. Other dopamine-mediated disease such as Parkinsonism and tardive dyskinesias can also be treat directly or indirectly by modulation of dopamine receptors. Compounds of the invention
15 are also useful in the treatment of depression, memory-impariment or Alzheimer's disease by modulation of D₄ receptors since these receptors are localized in areas known to control emotion and cognitive functions.

The invention also provides pharmaceutical compositions
20 comprising compounds of the invention, including packaged pharmaceutical compositions for treating, for example, disorders responsive to dopamine receptor modulation, especially dopamine D₄ receptor modulation, e.g., treatment of schizophrenia, depression, tardive diskinesia or cognitive
25 impairment by dopamine D₄ receptor modulation. The packaged pharmaceutical compositions include a container holding a defined amount or unit dose, e.g., a therapeutically effective amount, of at least one compound of the invention and instructions (e.g., labeling) indicating how the contained
30 compound is to be used in the patient for treating a disorder that is, for example, responsive to dopamine receptor modulation.

The present invention also pertains to methods of inhibiting the binding of dopamine to dopamine D₄ receptors

which methods involve contacting a compound of the invention with cells expressing dopamine D₄ receptors, wherein the compound is present at a concentration sufficient to inhibit dopamine binding to dopamine D₄ receptors *in vitro*. These methods include inhibiting the binding of dopamine to dopamine D₄ receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of dopamine to dopamine D₄ receptors *in vitro*. The amount of a compound that would be sufficient to inhibit the binding of dopamine to the dopamine D₄ receptor may be readily determined via a dopamine receptor binding assay, such as the assay described in Example 5. The dopamine receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of rat striatal homogenates or from cells expressing cloned human or monkey dopamine D₄ receptors, especially CHO (Chinese hamster ovary) cells expressing such receptors.

The compound of this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the dopamine D₄ receptor.

Radiolabeled derivatives of the compounds of the invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT).

Definitions

Where the compounds of the present invention have asymmetric centers, this invention includes all of the optical isomers and mixtures thereof.

Compounds with carbon-carbon double bonds may occur in Z- and E- forms, and all isomers of the compounds are included in the present invention.

When any variable (e.g. C₁₋₆ alkyl, C₁₋₈ alkyl, A, R₁, R₂, or R₃) occurs more than one time in Formula I, its definition at each occurrence is independent of its definition at every other occurrence.

5 By "C₁-C₆ alkyl" or "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms. Examples of alkyl groups include, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Preferred C₁-C₆ alkyl groups are methyl, ethyl, 10 propyl, butyl.

By "C₁-C₆ hydrocarbyl", "lower hydrocarbyl" and "hydrocarbyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, optionally 15 containing one or more carbon-carbon double or triple bonds. C₁-C₆ hydrocarbyl includes C₁-C₆ alkenyl, C₁-C₆ alkyl, and C₁-C₆ alkynyl. Examples of hydrocarbyl groups include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 20 3-hexyl, 3-methylpentyl, vinyl, 2-pentene, and propargyl. When reference is made herein to C₁-C₆ hydrocarbyl containing one or two double or triple bonds it is understood that at least two carbons are present in the alkyl for one double or triple bond, and at least four carbons for two double or triple bonds.

25 By "C₁-C₆ alkoxy" or "lower alkoxy" in the present invention is meant an alkyl group of indicated number of carbon atoms attached to the parent molecular moiety through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 30 3-methylpentoxy. Preferred alkoxy groups herein are C₁-C₄ alkoxy groups.

The terms "C₃-C₇ cycloalkyl" and "cycloalkyl" as used herein refer to cyclic alkyl groups having from 3-7 carbon

atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cycloheptyl, and cyclopentyl. These cycloalkyl groups may optionally be substituted with C₁-C₆ alkyl groups, preferably, methyl, ethyl, or propyl.

5 The term "cycloalkylalkyl," as used herein, refers to a C₃-C₆ cycloalkyl group attached to the parent molecular moiety through an alkyl group, as defined above. Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

10 The term "halogen" indicates fluorine, chlorine, bromine, or iodine.

 The term "nitrogen protecting group," as used herein, refers to groups known in the art that are readily introduced on to and removed from a nitrogen. Examples of nitrogen
15 protecting groups include Boc, Cbz, benzoyl, and benzyl. See also "Protective Groups in Organic Synthesis", 2nd Ed., Greene, T. W. and related publications.

Pharmaceutical Preparations

20 Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutically acceptable prodrugs of the compounds encompassed by Formula I. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically
25 acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, mineral oil, vegetable oil, and dimethylsulfoxide.

 The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or
30 rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes

subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of

5 general Formula I and a pharmaceutically acceptable carrier.

One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical

10 compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

15 Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and
20 preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents,

25 such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

30 The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral

preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among

the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland
5 fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories, e.g., for rectal
10 administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene
15 glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as
20 local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For administration to non-human animals, the compound or a composition containing the compound may be added to the animal's feed or drinking water. Also, it will be convenient
25 to formulate animal feed and drinking water products so that the animal takes in an appropriate quantity of the compound in its diet. It will further be convenient to present the compound in a composition as a premix for addition to the feed or drinking water.

30 Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to

produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

5 Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of schizophrenia, depression, or cognitive impairment a dosage regimen of 1 or 2
10 times daily is particularly preferred.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time
15 of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Preferred compounds of the invention will have desirable pharmacological properties that include, but are not limited to
20 oral bioavailability, low toxicity, low serum protein binding and desirable in vitro and in vivo half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

25 Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity.
30 Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by

Oravcová, et al. (Journal of Chromatography B (1996) volume 677, pages 1-27).

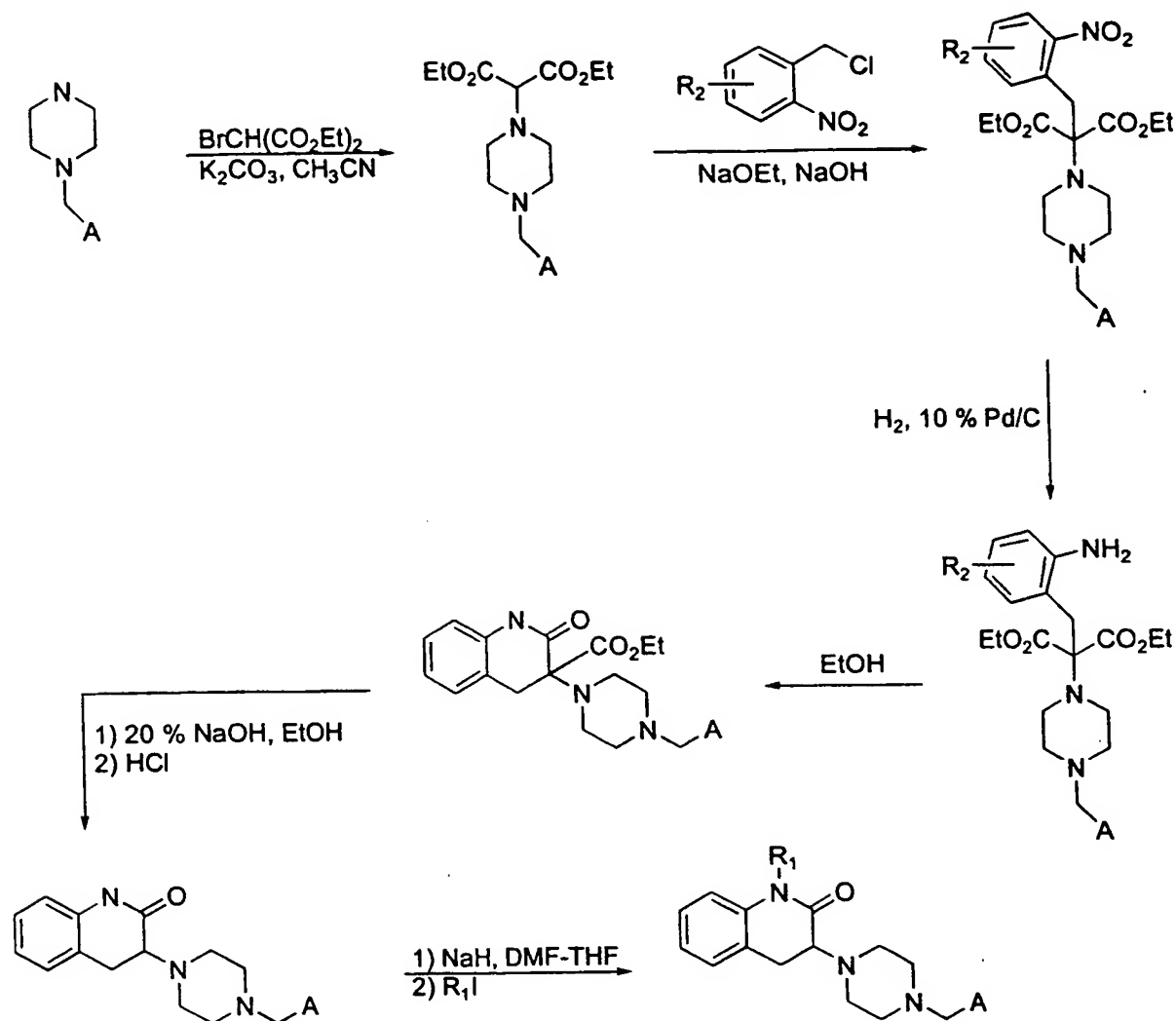
Compound half-life is inversely proportional to the frequency of dosage of a compound. In vitro half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

Preparation of compounds

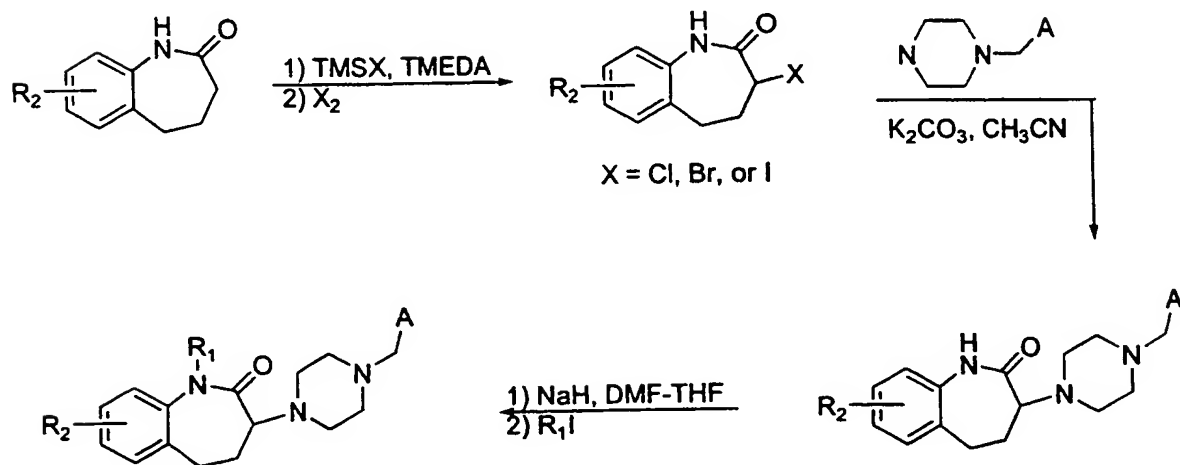
Representative syntheses of the compounds of the invention are presented in Schemes 1, 2, 3, and 4. Those having skill in the art will recognize that the starting materials and reaction conditions may be varied, the order in which the reactions are conducted may be altered, and additional steps may be employed to produce compounds encompassed by the present invention.

Scheme 1

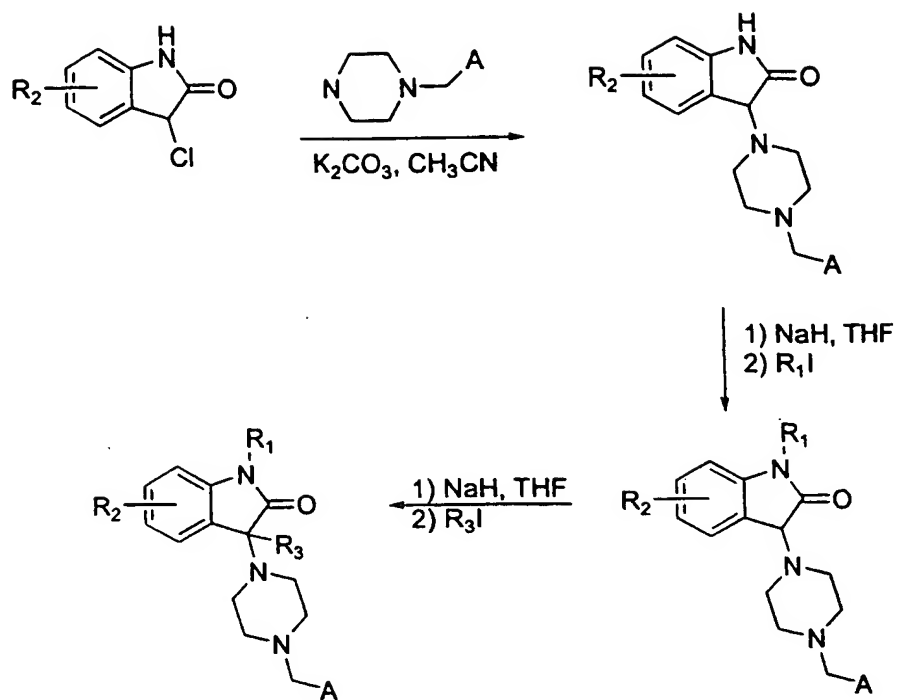


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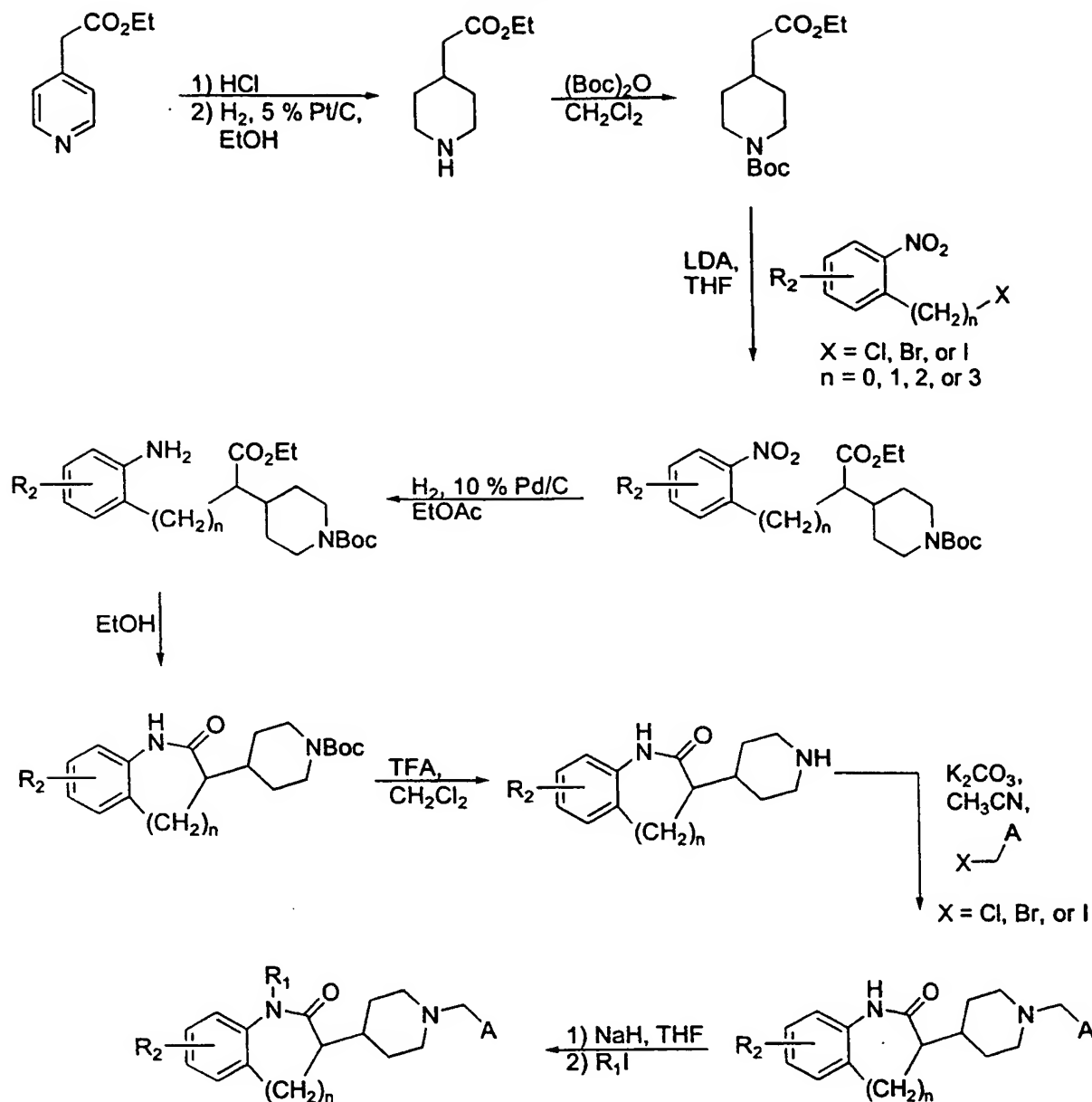
Scheme 2



Scheme 3



Scheme 4



In the above schemes, the various substituents are as defined for Formula I. The starting material in Scheme 3 can be prepared using the same method as in Scheme 2.

The starting materials used herein are either commercially available, known, or capable of being prepared by methods known in the art, i.e., literature methods. Further, those skilled in the art will recognize how to modify literature procedures to prepare the desired starting materials. Unless otherwise specified all reagents and solvents are of standard commercial

grade and are used without further purification. In some cases, protection of reactive functionalities may be necessary to achieve some of the desired transformations. In general, such need for protecting groups, as well as the conditions necessary to attach and remove such groups, will be apparent to those skilled in the art of organic synthesis.

EXAMPLE 1

10 3-{4-[(4-Chlorophenyl)methyl]piperazin-1-yl}-1-methyl-1,2,3,4-tetrahydroquinolin-2-one, Compound 1a.

Part A: Diethyl 2-{4-[(4-chlorophenyl)methyl]piperazin-1-yl}malonate

15

To a solution of 3.6 g of diethyl bromomalonate in 100 mL of acetonitrile is added 3.12 g of potassium carbonate and 3.15 g of 1-[(4-chlorophenyl)methyl] piperazine. This mixture is stirred at room temperature for about 18 h. The reaction mixture is filtered through silica gel and the filtrate is concentrated under reduced pressure, then dried in vacuo to provide 5.4 g of product as a light yellow syrup. ¹HNMR (CDCl₃) δ 7.26-7.25 (m, 4H), 4.23 (q, J = 7.2 Hz, 4H), 4.02 (s, 1H), 3.45 (s, 2H), 2.77 (t, J = 4.8 Hz, 4H), 2.50 (t, J = 4.8 Hz, 4H), 1.28 (t, J = 7.2 Hz, 6H); LC-MS (APCI, m/z) 367 (M+1)⁺.

25

Part B: Diethyl 2-{4-[(4-chlorophenyl)methyl]piperazinyl}-2-[(2-nitrophenyl)methyl]malonate

30 Example 1A (3.7 g) is added to a stirred solution of sodium ethoxide in ethanol (prepared from 230 mg of sodium and 25 mL of ethanol). After 30 min, 1.71 g of 2-nitrobenzyl chloride is added and the solution is stirred under reflux for about 15 h. The solvent is then removed under reduced pressure,

and the product partitioned between ethyl acetate and water. The layers are separated and the ethyl acetate is dried over sodium sulfate, filtered and concentrated to afford an oil which is purified by silica gel chromatography using
5 chloroform/methanol (1:20) as the eluent to give 2.5 g of the product as a syrup. ¹HNMR (CDCl₃) δ 7.58-7.21 (m, 8H), 4.11 (q, J = 7.2 Hz, 4H), 3.78 (s, 2H), 3.71 (s, 2H), 2.79-2.76 (m, 4H), 2.50-2.44 (m, 4H), 1.18 (t, J = 7.2 Hz, 6H); LC-MS (APCI, m/z) 504 (M+1)⁺.

10

Part C: Diethyl 2-[(2-aminophenyl)methyl]-2-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]malonate

A mixture of 250 mg of Example 1B and 25 mg of 10% Pd/C in
15 30 mL of room temperature ethyl acetate is hydrogenated at atmospheric pressure until uptake of hydrogen ceased (approx. 24 h). The reaction mixture is filtered through celite, the filtrate is concentrated under reduced pressure at temperatures below 30°C, and then dried in vacuo to give 210 mg of product
20 as a viscous oil. ¹HNMR (CDCl₃) δ 7.26 (m, 8H), 4.13 (q, J = 7.2 Hz, 4H), 3.47 (s, 2H), 3.38 (s, 2H), 2.77 (m, 4H), 2.55 (m, 4H), 1.64 (s, 2H), 1.17 (t, J = 7.2 Hz, 6H); LC-MS (APCI, m/z) 474 (M+1)⁺.

25 Part D: Ethyl 3-[4-[(4-chlorophenyl)methyl]piperazinyl]-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate

A solution of 474 mg of Example 1C in 10 mL of ethanol is refluxed for about 4 h. The solvent is removed under reduced
30 pressure, affording a residue which is dried in vacuo to give 410 mg of the desired product as a viscous oil. ¹HNMR (CDCl₃) δ 7.28-7.10 (m, 8H), 4.12 (q, J = 7.2 Hz, 2H), 3.86 (s, 2H), 3.24 (s, 2H), 2.84-2.78 (m, 4H), 2.33 (m, 4H), 1.17 (t, J = 7.2 Hz, 6H); LC-MS (APCI, m/z) 428 (M+1)⁺.

Part E: 3-{4-[(4-Chlorophenyl)methyl]piperazinyl} -1,2,3,4-tetrahydroquinolin-2-one, Compound 1h.

5 4 mL of 20% sodium hydroxide and 428 mg of Example 1D in 10 mL of methanol, are refluxed for 18 h. The reaction mixture is cooled to room temperature, neutralized with 6N hydrochloric acid to pH about 6 ~ 7. The methanol is evaporated, and the residue is partitioned between chloroform and water. The layers
10 are separated and the chloroform is dried, filtered and concentrated to afford a viscous oil which is then purified by silica gel chromatography using chloroform/methanol (1:20) as the eluent. 315 mg of the desired product is obtained as a colorless solid. mp 153-155 °C; ¹HNMR (CDCl₃) δ 7.63-7.38 (m, 2H), 7.26-7.16 (m, 4H), 7.03-6.98 (m, 1H), 6.75-6.73 (m, 1H),
15 4.02 (s, 2H), 3.57 (t, J = 8.2 Hz, 1H), 3.08 (d, J = 8.2 Hz, 2H), 2.88 (m, 4H), 2.80 (m, 4H); LC-MS (APCI, m/z) 367 (M+1)⁺. A portion of the product is converted to the dihydrochloride salt, mp 265-266 °C (2 HCl).

20

Part F: 3-{4-[(4-chlorophenyl)methyl]piperazinyl} -1-methyl-1,2,3,4-tetrahydroquinolin-2-one, Compound 1a.

To a suspension of 50 mg of sodium hydride (60% oil
25 dispersion) in 20 mL of anhydrous, room temperature tetrahydrofuran is added dropwise a solution of 350 mg of Example 1E in 5 mL of anhydrous tetrahydrofuran. The reaction mixture is stirred for 1 h, and then 280 mg of iodomethane is added. After the reaction mixture is stirred for an additional
30 5 h, 5 mL of water is slowly added. The product is extracted several times with dichloromethane and the combined dichloromethane extracts are washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed under reduced pressure, and the resulting residue is purified

by silica gel chromatography using chloroform/methanol (1:100) as the eluent. 320 mg of the desired product is obtained as a viscous oil. ¹HNMR (CDCl₃) δ 7.26-7.21 (m, 2H), 7.15 (d, J = 7.2 Hz, 2H), 7.02-6.96 (m, 2H), 6.94 (d, J = 7.2 Hz, 2H), 3.44 (s, 2H), 3.38 (t, J = 9.8 Hz, 1H), 3.34 (s, 3H), 3.01 (d, J = 9.9 Hz, 2H), 2.76-2.71 (m, 4H), 2.44 (m, 4H); LC-MS (APCI, m/z) 356 (M+1)⁺. A portion of the product is converted to the dihydrochloride salt, mp 251-253 °C (isopropanol-ethyl acetate).

EXAMPLE 2

3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1-methyl-3H,4H,5H-benzo[f]azepin-2-one

15 Part A: 3-Iodo-1H,3H,4H,5H-benzo[f]azepin-2-one

To a solution of 3 g of 1H,3H,4H,5H-benzo[f]azepin-2-one in 30 mL of anhydrous dichloromethane at 0°C under argon is added 8.4 mL of N,N,N',N'-tetramethylethylenediamine (TMEDA) and 7.8 mL of trimethylsilyl iodine. After 30 min, 7.2 g of solid iodine is added in one portion, and the reaction mixture is stirred at 0°C for about an additional 1h. The reaction mixture is then diluted with 100 mL of dichloromethane, and quenched by addition of excess aqueous sodium sulfite. The product is extracted several times with dichloromethane and the combined dichloromethane extracts are washed with brine, dried over anhydrous sodium sulfate, and filtered to give a light yellow solid. The solid is purified by silica gel chromatography using hexanes/ethyl acetate (1:3) as the eluent to afford 4.5 g of the desired product as a colorless solid. mp 175-176 °C; ¹HNMR (CDCl₃) δ 7.63 (m, 1H), 7.31-7.17 (m, 2H), 7.01 (d, J = 7.8 Hz, 1H), 4.68 (t, J = 8.8 Hz, 1H), 3.01-2.93 (m, 1H), 2.81-2.66 (m, 3H); LC-MS (APCI, m/z) 288 (M+1)⁺.

Part B: 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-
1H,3H,4H,5H-benzo[f]azepin-2-one

5 574 mg of 3-iodo-1H,3H,4H,5H-benzo[f]azepin-2-one, 400 mg
of potassium carbonate and 420 mg of [(4-
chlorophenyl)methyl]piperazine are refluxed in 25 mL of
acetonitrile for about 4 h. The reaction mixture is filtered
though silica gel, concentrated under reduced pressure and
purified by silica gel chromatography using chloroform/methanol
10 (1:100) as the eluent. The product is then crystallized from
ethyl acetate and hexanes to give 601 mg of a colorless solid.
mp 74-75 °C; ¹HNMR (CDCl₃) δ 7.24-7.10 (m, 6H), 6.95 (d, J = 9.0
Hz, 2H), 3.44 (s, 2H), 3.10-3.04 (m, 1H), 2.93-2.87 (m, 1H),
2.72 (m, 1H), 2.66 (m, 4H), 2.46 (m, 4H), 2.32-2.26 (m, 2H);
15 LC-MS (APCI, m/z) 367 (M+1)⁺.

Part C: 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1-methyl-
3H,4H,5H-benzo[f]azepin-2-one, Compound 1e.

20 A solution of 140 mg of 3-{4-[(4-
chlorophenyl)methyl]piperazinyl}-1H,3H,4H,5H-benzo[f]azepin-2-
one in 5 mL of anhydrous tetrahydrofuran is added to a
suspension of 20 mg of sodium hydride (60% oil dispersion) in 8
mL of anhydrous, room temperature tetrahydrofuran. . The
25 reaction mixture is stirred for 1 h, and then 112 mg of
iodomethane is added. After stirring for an additional 5 h, 5
mL of water is added. The product is then extracted several
times with dichloromethane and the combined dichloromethane
extracts are washed with brine, dried over anhydrous sodium
30 sulfate, and filtered. The solvent is removed under reduced
pressure and the resulting residue is purified by silica gel
chromatography using chloroform/methanol (1:100) as the eluent.
135 mg of the desired product is obtained as a viscous oil.
¹HNMR (CDCl₃) δ 7.32-7.13 (m, 8H), 3.45 (s, 2H), 3.35 (s, 3H),

3.04-2.98 (m, 1H), 2.71-2.59 (m, 4H), 2.47 (m, 2H), 2.30-2.16 (m, 2H), 1.75-1.64 (m, 2H), 1.53-1.43 (m, 2H); LC-MS (APCI, m/z) 384 (M+1)⁺. A portion of the product is converted to the dihydrochloride salt, mp 275-277 °C. (isopropanol-ethyl acetate).

EXAMPLE 3

10 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1-methylindolin-2-one

Part A: 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}indolin-2-one

15 510 mg of 3-chloroindolin-2-one, 600 mg of potassium carbonate, and 630 mg of [(4-chlorophenyl)methyl]piperazine are stirred in 35 mL of room temperature acetonitrile for about 15 h. The reaction mixture is filtered through silica gel, and concentrated under reduced pressure. The resulting residue is
20 crystallized from ethyl acetate and hexanes to give 620 mg of the desired product as a colorless solid. mp 169-170 °C; ¹HNMR (CDCl₃) δ 7.83 (m, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.26-7.25 (m, 4H), 7.23-7.20 (m, 1H), 7.06-7.01 (m, 1H), 6.82 (d, J = 7.8 Hz, 1H), 4.29 (s, 1H), 3.47 (s, 2H), 2.88 (m, 2H), 2.97-2.72 (m,
25 2H), 2.47 (m, 4H); LC-MS (APCI, m/z) 342 (M+1)⁺.

Part B: 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1,3-dimethylindolin-2-one, Compound 1f.

30

A solution of 100 mg of 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}indolin-2-one in 2 mL of anhydrous tetrahydrofuran is added dropwise to a suspension of 38 mg of sodium hydride (60% oil dispersion) in 5 mL of

anhydrous, room temperature tetrahydrofuran. The reaction mixture is stirred for 1 h, and then 84 mg of iodomethane is added. After the mixture is stirred for 5 more hours, 4 mL of water is added. The reaction mixture is extracted several times with dichloromethane, and the combined dichloromethane extracts are washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed under reduced pressure and the resulting residue is purified by silica gel chromatography using chloroform as the eluent. The chromatographed material is then crystallized from ethyl acetate and hexanes to give 89 mg of the desired product. ¹HNMR (CDCl₃) δ 7.30-7.19 (m, 6H), 7.08-7.03 (m, 1H), 6.81 (d, J = 8.1 Hz, 1H), 3.42 (s, 2H), 3.18 (s, 3H), 2.67-2.63 (m, 4H), 2.41 (m, 4H), 1.49 (s, 3H); LC-MS (APCI, m/z) 370 (M+1)⁺. A portion of the product is converted to the dihydrochloride salt, mp 145°C (dec.) (isopropanol-ethyl acetate).

Example 4

The following compounds are prepared essentially according to the procedures set forth above in Schemes 1-4 and Examples 1-4.

(a) 3-{4-[(4-chlorophenyl)methyl]piperazinyl}-1-methyl-1,2,3,4-tetrahydroquinolin-2-one;

(b) 3-{4-[(4-chlorophenyl)methyl]piperazinyl}-1-ethyl-1,2,3,4-tetrahydroquinolin-2-one. mp 249-251 °C (2HCl); ¹HNMR (CDCl₃) δ 7.30-7.13 (m, 6H), 6.96 (d, J = 7.5 Hz, 2H), 4.05-3.84 (m, 1H), 3.44 (s, 2H), 3.39-3.33 (m, 2H), 2.98-2.94 (m, 2H), 2.80-2.75 (m, 2H), 2.69-2.65 (m, 2H), 2.46 (m, 2H), 1.68 (q, J = 7.6 Hz, 2H), 1.01 (t, J = 7.6 Hz, 3H); LC-MS (APCI, m/z) 384 (M+1)⁺;

(c) 3-{4-[(4-methylphenyl)methyl]piperazinyl}-1-methyl-
1,2,3,4-tetrahydroquinolin-2-one;

(d) 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1,3-
5 diethylindolin-2-one. mp 133 °C (2 HCl, dec.); ¹HNMR (CDCl₃) δ
7.29-7.18 (m, 6H), 7.04 (td, J = 7.2, 1.1 Hz, 1H), 6.81 (dd, J
= 8.6, 1.1 Hz, 1H), 3.73 (q, J = 7.2 Hz, 1H), 3.41 (s, 2H),
2.67-2.64 (m, 4H), 2.39 (m, 4H), 1.97 (q, J = 7.6 Hz, 2H), 1.22
(t, J = 7.2 Hz, 3H), 0.62 (t, J = 7.6 Hz, 3H); LC-MS (APCI,
10 m/z) 398 (M+1)⁺;

(e) 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1-methyl-
3H,4H,5H-benzo[f]azepin-2-one;

(f) 3-{4-[(4-Methylphenyl)methyl]piperazinyl}-1-methyl-
15 3H,4H,5H-benzo[f]azepin-2-one. mp 217-219 °C (2HCl); ¹HNMR
(CDCl₃) δ 7.29-7.09 (m, 8H), 3.39-3.36 (m, 2H), 3.34 (s, 2H),
3.04-2.97 (m, 1H), 2.77-2.56 (m, 8H), 2.31 (s, 3H), 1.53-1.41
(m, 2H), 1.02 (d, J = 7.2 Hz, 3H); LC-MS (APCI, m/z) 364
20 (M+1)⁺;

(g) 3-{4-[(4-Methylphenyl)methyl]piperazinyl}-1-ethyl-
3H,4H,5H-benzo[f]azepin-2-one. mp 228-230 °C (2HCl); ¹HNMR
(CDCl₃) δ 7.32-7.15 (m, 6H), 7.09 (d, J = 7.8 Hz, 2H), 4.30-
25 4.23 (m, 1H), 3.46 (s, 2H), 2.96-2.73 (m, 2H), 2.62-2.50 (m,
8H), 2.32 (s, 3H), 2.24-2.14 (m, 2H), 1.28-1.24 (m, 2H), 1.12
(d, J = 7.2 Hz, 3H); LC-MS (APCI, m/z) 378 (M+1)⁺;

(h) 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1-ethyl-
30 3H,4H,5H-benzo[f]azepin-2-one. mp 249-251 °C (2HCl); ¹HNMR
(CDCl₃) δ 7.30-7.13 (m, 6H), 6.96 (d, J = 7.5 Hz, 2H), 4.05-
3.84 (m, 1H), 3.44 (s, 2H), 3.39-3.33 (m, 2H), 2.98-2.94 (m,
2H), 2.80-2.75 (m, 2H), 2.69-2.65 (m, 2H), 2.46 (m, 2H), 1.68

(q, $J = 7.6$ Hz, 2H), 1.01 (t, $J = 7.6$ Hz, 3H); LC-MS (APCI, m/z) 384 (M+1)⁺;

(i) 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1-isopropyl-3H,4H,5H-benzo[f]azepin-2-one. mp 234-236 °C (2HCl);
5 ¹HNMR (CDCl₃) δ 7.26-7.14 (m, 8H), 4.90-4.81 (m, 1H), 3.45 (s, 2H), 3.40-3.34 (m, 2H), 2.87-2.73 (m, 2H), 2.64-2.54 (m, 4H), 2.21-2.04 (m, 2H), 1.54-1.44 (m, 1H), 1.42 (d, $J = 7.0$ Hz, 3H), 1.05 (d, $J = 7.0$ Hz, 3H); LC-MS (APCI, m/z) 412 (M+1)⁺;

10 (j) 3-{4-[(4-Methylphenyl)methyl]piperazinyl}-1-isopropyl-3H,4H,5H-benzo[f]azepin-2-one. mp 180-183 °C (2HCl);
¹HNMR (CDCl₃) δ 7.26-7.07 (m, 6H), 7.08 (d, $J = 7.5$ Hz, 2H), 4.91-4.82 (m, 1H), 3.44 (s, 2H), 3.39-3.34 (m, 1H), 2.83-2.73
15 (m, 2H), 2.55 (m, 4H), 2.48 (m, 4H), 2.30 (s, 3H), 2.08-2.18 (m, 2H), 1.42 (d, $J = 7.0$ Hz, 3H), 1.05 (d, $J = 7.2$ Hz, 3H); LC-MS (APCI, m/z) 392 (M+1)⁺;

(k) 3-{1-[(4-chlorophenyl)methyl]piperazin-4-yl}-1-methyl-1,2,3,4-tetrahydroquinolin-2-one.
20

Example 5

Determination of dopamine D₂ and D₄ receptor binding activity

The following assay is a standard assay for determining
25 the binding affinity of compounds to dopamine D₄ and D₂ receptors.

Pellets of Chinese hamster ovary (CHO) cells containing recombinantly produced primate D₂, human D₄ and human α1 receptors are used for the assays. The sample is homogenized
30 in 100 volumes (w/vol) of 0.05 M Tris HCl buffer containing 120 mM NaCl, 5 mM MgCl₂ and 1 mM EDTA at 4°C and pH 7.4. The sample is then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample is then recentrifuged at 30,000 x g, the supernatant is decanted, and the final tissue sample is

frozen until use. The tissue is resuspended 1:20 (wt/vol) in 0.05 M Tris HCl buffer containing 120 mM NaCl.

Incubations for dopaminergic binding are carried out at 25°C and contain 0.4 ml of tissue sample, 0.1 nM ³H-YM 09151-2 (Nemonapride, cis-5-Chloro-2-methoxy-4-(methylamino)-N-(2-methyl-2-(phenylmethyl)-3-pyrrolidinyl)benzamide) and the compound of interest in a total incubation volume of 1.0 ml. Nonspecific binding is defined as that binding found in the presence of 1 μM spiperone; without further additions, nonspecific binding is less than 20% of total binding.

Binding characteristics for Compound 1a for D₂ and D₄ receptor subtypes are shown in Table 2 for primate or human dopamine receptor subtypes.

Table 2

Compound Number ¹	D ₂ K _i (nM)	D ₄ K _i (nM)
1a	144	6
1c	21	4
1h	1373	100

Preferred compounds of the invention exhibit K_i values of less than 500 nM at the dopamine D₄ receptor, more preferred compounds exhibit K_i values of less than 100 nM and most preferred compounds of the invention exhibit K_i values of less than 20 nM. Preferred compounds of the invention also exhibit greater than 20-fold selectivity for the dopamine D₄ receptor over the dopamine D₂ receptor; more preferred compounds of the invention exhibit greater than 100-fold selectivity for the dopamine D₄ receptor over the dopamine D₂ receptor.

Example 6

Preparation of radiolabeled probe compounds of the invention

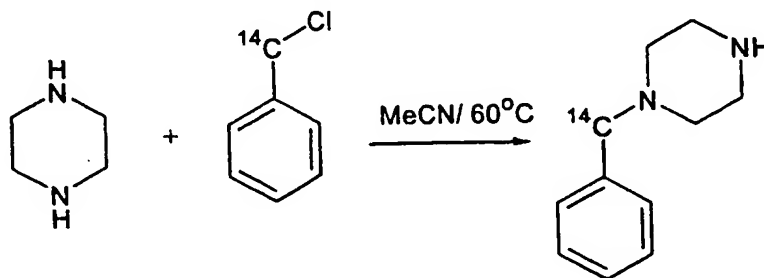
The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using

precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^3H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; and Moravsek Biochemicals Inc., Brea, CA.

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Tritium labeled probe compounds can also be prepared, when appropriate, by sodium borotritide reduction. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate.

Example 6a

In addition to the method described above radiolabeled compounds of the invention may be prepared by a variety of other synthetic methods. For example benzyl-piperazine starting material may be prepared as follows using ARC-563 benzyl chloride, [$7\text{-}^{14}\text{C}(\text{U})$], supplied by American Radiolabeled Chemicals, Inc., St. Louis, MO, as the radioisotope precursor.



The labeled benzyl-piperazine may be used to prepare compounds of the invention via the general method of Scheme I.

Example 7

5 Use of compounds of the invention as probes for Dopamine receptors in cultured cells and tissue samples

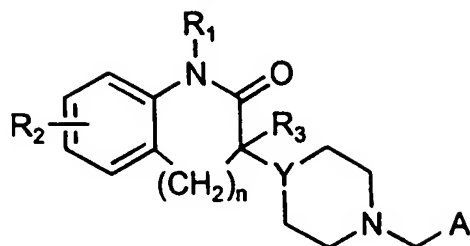
Receptor autoradiography (receptor mapping) of dopamine receptors in cultured cells or tissue samples is carried out in vitro as described by Kuhar in sections 8.1.1 to 8.1.9 of
10 Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example.

The invention and the manner and process of making and
15 using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein
20 without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

Claims

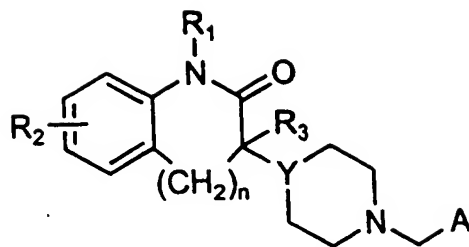
What is claimed is:

1. A compound of the formula:



- 5 or a pharmaceutically acceptable salt thereof, wherein
 A represents phenyl, optionally substituted with up to four
 substituents selected from halogen, hydroxy, amino, mono-
 or di(C₁-C₆)hydrocarbylamino, aminosulfonyl, C₁-C₆
 hydrocarbylaminosulfonyl, di(C₁-
 10 C₆)hydrocarbylaminosulfonyl, cyano, nitro,
 cyclohydrocarbylhydrocarbyl, trifluoromethyl, C₁-C₆
 hydrocarbyl, trifluoromethoxy, C₃-C₆ cyclohydrocarbyl, and
 C₁-C₆ alkoxy;
 R₁ is hydrogen, cyclohydrocarbylhydrocarbyl, C₁-C₆ hydrocarbyl,
 15 or alkanoyl;
 R₃ is hydrogen, alkoxycarbonyl, aryloxy carbonyl, carboxyl,
 carboxamido, mono or dihydrocarbylamino carbonyl,
 arylhydrocarbyl, or C₁-C₆ hydrocarbyl;
 R₂ represents hydrogen, halogen, hydroxy, amino, mono- or
 20 di(C₁-C₆)hydrocarbylamino, aminosulfonyl, mono or di(C₁-
 C₆)hydrocarbylaminosulfonyl, cyano, nitro,
 cyclohydrocarbylhydrocarbyl, trifluoromethyl, C₁-C₆
 hydrocarbyl, trifluoromethoxy, C₃-C₆ cyclohydrocarbyl, and
 C₁-C₆ alkoxy;
 25 n is 0 or an integer chosen from 1 or 2;
 Y is nitrogen or CH.

2. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein

A represents phenyl, optionally substituted with up to four
substituents selected from halogen, hydroxy, amino, mono-
or di(C₁-C₆)alkylamino, aminosulfonyl, C₁-C₆
alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, cyano,
nitro, cycloalkylalkyl, trifluoromethyl, C₁-C₆ alkyl,
trifluoromethoxy, C₃-C₆ cycloalkyl, and C₁-C₆ alkoxy;

R₁ is hydrogen, cycloalkylalkyl, C₁-C₆ alkyl, or C₁-C₆ alkanoyl;

R₃ is hydrogen, alkoxycarbonyl, aryloxycarbonyl, carboxyl,
carboxamido, mono or dialkylaminocarbonyl, arylalkyl, or
C₁-C₆ alkyl;

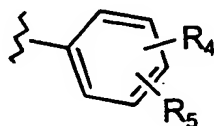
R₂ represents hydrogen, halogen, hydroxy, amino, mono- or
di(C₁-C₆)alkylamino, aminosulfonyl, mono or di(C₁-
C₆)alkylaminosulfonyl, cyano, nitro, cycloalkylalkyl,
trifluoromethyl, C₁-C₆ alkyl, trifluoromethoxy, C₃-C₆
cycloalkyl, and C₁-C₆ alkoxy;

n is 0 or an integer chosen from 1 or 2;

Y is nitrogen or CH.

3. A compound according to claim 1 wherein X is CH.

4. A compound according to claim 3, wherein A is a group
of the formula:



wherein R₄ and R₅ independently represent hydrogen halogen,
hydroxy, amino, mono- or di(C₁-C₆)alkylamino, aminosulfonyl, C₁-
C₆ alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, cyano,

nitro, cycloalkylalkyl, trifluoromethyl, C₁-C₆ alkyl, trifluoromethoxy, C₃-C₆ cycloalkyl, and C₁-C₆ alkoxy.

5. A compound according to claim 4 wherein

5 R₁ is C₁-C₃ alkyl;

R₂ and R₃ are independently hydrogen or C₁-C₆ alkyl;

R₄ and R₅ are independently hydrogen, halogen, C₁-C₆ alkyl, or C₁-C₆ alkoxy, provided that not both R₄ and R₅ are hydrogen; and

10 n is 1.

6. A compound according to claim 5, wherein R₂ and R₃ are both hydrogen.

15 7. A compound according to claim 6, wherein R₁ is C₁-C₂ alkyl.

8. A compound according to claim 7, wherein R₁ is methyl.

20

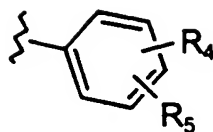
9. A compound according to claim 8, wherein R₄ and R₅ independently hydrogen, chloro, fluoro, bromo, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

25 10. A compound according to claim 9 wherein not both R₄ and R₅ are hydrogen simultaneously.

11. A compound according to claim 1, wherein X is nitrogen.

30

12. A compound according to claim 10, wherein A is a group of the formula:



wherein R₄ and R₅ independently represent hydrogen halogen, hydroxy, amino, mono- or di(C₁-C₆)alkylamino, aminosulfonyl, C₁-C₆ alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, cyano, nitro, cycloalkylalkyl, trifluoromethyl, C₁-C₆ alkyl, trifluoromethoxy, C₃-C₆ cycloalkyl, and C₁-C₆ alkoxy.

13. A compound according to claim 12 wherein R₁ is C₁-C₃ alkyl; R₂ and R₃ are independently hydrogen or C₁-C₆ alkyl; R₄ and R₅ are independently hydrogen, halogen, C₁-C₆ alkyl, or C₁-C₆ alkoxy, provided that not both R₄ and R₅ are hydrogen; and n is 1.

14. A compound according to claim 13, wherein R₂ and R₃ are both hydrogen.

15. A compound according to claim 14, wherein R₁ is C₁-C₂ alkyl.

16. A compound according to claim 15, wherein R₁ is methyl.

17. A compound according to claim 16, wherein R₄ and R₅ independently hydrogen, chloro, fluoro, bromo, C₁-C₃ alkyl, or C₁-C₃ alkoxy.

18. A compound according to claim 17 wherein not both R₄ and R₅ are hydrogen simultaneously.

19. A compound according to claim 1 which is 3-{4-[(4-chlorophenyl)methyl]piperazinyl}-1-methyl-1,2,3,4-tetrahydroquinolin-2-one.

5 20. A compound according to claim 1 which is 3-{4-[(4-methylphenyl)methyl]piperazinyl}-1-methyl-1,2,3,4-tetrahydroquinolin-2-one.

21. A compound according to claim 1 which is 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1,3-dimethylindolin-2-one.
10

22. A compound according to claim 1 which is 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1,3-diethylindolin-2-one.

15 23. A compound according to claim 1 which is 3-{4-[(4-Methylphenyl)methyl]piperazinyl}-1-methyl-3H,4H,5H-benzo[f]azepin-2-one.

24. A compound according to claim 1 which is 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1-methyl-3H,4H,5H-benzo[f]azepin-2-one.
20

25. A compound according to claim 1 which is 3-{4-[(4-Methylphenyl)methyl]piperazinyl}-1-ethyl-3H,4H,5H-benzo[f]azepin-2-one.
25

26. A compound according to claim 1 which is 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1-ethyl-3H,4H,5H-benzo[f]azepin-2-one.

30

27. A compound according to claim 1 which is 3-{4-[(4-Chlorophenyl)methyl]piperazinyl}-1-isopropyl-3H,4H,5H-benzo[f]azepin-2-one.

28. A compound according to claim 1 which is 3-{4-[(4-Methylphenyl)methyl]piperazinyl}-1-isopropyl-3H,4H,5H-benzo[f]azepin-2-one.

5 29. A compound according to claim 1 which is 3-{1-[(4-chlorophenyl)methyl]piperazin-4-yl}-1-methyl-1,2,3,4-tetrahydroquinolin-2-one.

10 30. A compound according to claim 1 which is 3-{4-[(4-chlorophenyl)methyl]piperazinyl}-1,2,3,4-tetrahydroquinolin-2-one.

31. A pharmaceutical composition comprising a compound according to Claim 1, together with at least one
15 pharmaceutically acceptable carrier or excipient.

32. A method for the treatment or prevention of a disease or disorder associated with pathogenic dopamine receptor activation, said method comprising administering to a patient
20 in need of such treatment or prevention an effective amount of a compound of claim 1.

33. A method according to Claim 31 wherein the disease or disorder is schizophrenia, psychotic depression, mania,
25 Parkinson's disease, or tardive dyskinesia.

34. A method according to Claim 32 wherein the disease or disorder is attention deficit disorder or Alzheimer's disease.

30 35. A method according to Claim 33 wherein the disease or disorder is extrapyramidal side effects associated with the use of a neuroleptic agent.

36. The use of a compound according to Claim 1 for the manufacture of a medicament for the treatment or prevention of a disease or disorder associated with pathogenic dopamine receptor activation.

5

37. A method for localizing dopamine receptors in a tissue sample comprising:

contacting with the sample a detectably-labeled compound of claim 1 under conditions that permit binding of the compound to dopamine receptors,
washing the sample to remove unbound compound, and detecting the bound compound.

38. The method of Claim 37 wherein the Dopamine receptor is a D₄ receptor.

39. A method of inhibiting the binding of a dopamine to a dopamine receptor, said method comprising contacting a compound of claim 1 with cells expressing such a receptor in the presence of a dopamine, wherein the compound is present at a concentration sufficient to inhibit dopamine binding to cells expressing a cloned human dopamine receptor *in vitro*.

40. The method of claim 39 wherein the dopamine receptor is a dopamine D₄ receptor.

41. A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 31 in a container and instructions for using the composition to treat a patient suffering from a disorder responsive to dopamine receptor antagonism.

42. The packaged pharmaceutical composition of claim 41, wherein said patient is suffering from schizophrenia, psychotic

depression, mania, Parkinson's disease, or tardive dyskinesia, attention deficit disorder, Alzheimer's disease, or the extrapyramidal side effects associated with the use of a neuroleptic agent.

5

43. A compound according to claim 1 wherein in an assay of dopamine receptor binding the compound exhibits a K_i of 1 micromolar or less.

10

44. A compound according to claim 1 wherein the compound exhibits a K_i of 100 nanomolar or less.

45. A compound according to claim 1 wherein the compound exhibits a K_i of 10 nanomolar or less.

15

46. A compound according to Claim 1 wherein the compound exhibits a 20-fold greater affinity for the dopamine D_4 receptor than for the dopamine D_2 receptor in an assay of dopamine receptor binding.

20

47. A compound according to Claim 1 wherein the compound exhibits a 100-fold greater affinity for the dopamine D_4 receptor than for the dopamine D_2 receptor in an assay of dopamine receptor binding.

25

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/US 00/16784

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/38 C07D215/22 C07D223/16 C07D209/40 C07D209/34
C07D401/04 A61K31/404 A61K31/4704 A61K31/55 A61P25/00

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EPO-Internal, PAJ, CHEM ABS Data

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A	WO 97 23216 A (BIGGE CHRISTOPHER F ;WARNER LAMBERT CO (US); CAI SUI XIONG (US); L) 3 July 1997 (1997-07-03) examples 194,195,217,225,232,254,255 abstract; claims 16,27	1-4, 31, 33
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

4 October 2000

Date of mailing of the international search report

20/10/2000

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 4 855 302 A (GASC JEAN-CLAUDE ET AL) 8 August 1989 (1989-08-08) claims 1,5 ----	1-3,31
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Appl. No.

PCT/US 00/16784

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